

### **REMARKS / ARGUMENTS**

The Office Action mailed August 9, 2005, has been received and reviewed. Claims 1 through 20 were pending in the Application, and claims 1 through 15 were withdrawn from consideration as being directed to a non-elected invention. Claims 16 through 20 were rejected. Claims 1, 2, 3, 5, 6, 9, 11, 12, 14, 16 and 18 have been amended as shown above and new claims 21 through 34 have been added.

In the Specification, the paragraph on lines 8 through 16 of page 65 has been amended to correct obvious typographical errors.

Applicants hereby respectfully request reconsideration of the amended Application, and offer the following remarks for consideration by the examiner.

### **THE PRESENT INVENTION AND ITS ADVANTAGES**

The present invention provides novel methods and kits for altering levels of expression of a plurality of recombinantly expressed gene products using RNA interference (RNAi) induced by a single species of "Universal interfering RNA" (UiRNA). The UiRNA is directed towards a commonly-shared "Universal target RNA" (UtRNA) that is incorporated into a plurality of chimeric RNA transcripts comprising different subject RNAs that each encode a gene product (usually a protein) whose cellular concentration is to be decreased through RNAi. Optionally, the UtRNA may encode a readily detectable peptide tag (e.g., an epitope tag, fluorescent peptide, enzymatic tag, etc.) that can be expressed as part of a fusion protein that also comprises the polypeptide encoded by the subject RNA. Advantageously, such UtRNA-encoded peptide tags can be used to readily quantify the level of expression of the fusion protein under study. Importantly, the methods and kits of the present invention can be used to investigate the function of any number of gene products – and the more gene products being investigated at one time, the greater the benefits.

Among the many advantages provided by the methods and kits of the instant invention, perhaps the most significant is the ability to use a single species of interfering RNA to knock down the expression of a plurality of subject RNAs. This use of a UiRNA provides several specific advantages. For instance, it (a) obviates the need to design, manufacture and test distinct interfering RNAs that are specific to each subject RNA; (b)

controls for variation in “off-target” effects resulting from the use of different interfering RNAs targeting corresponding subject RNAs; and (c) greatly facilitates high-throughput RNA interference-based applications. Furthermore, in cells and organisms capable of “transitive RNAi,” the UirRNA can be used not only to knock down the expression of recombinantly-expressed gene products, but corresponding natural gene products encoded by endogenous transcripts of related sequence.

#### CLAIM AMENDMENTS AND ADDITIONS

Claims 1, 2, 3, 5, 6, 9, 11, 12, 14, 16 and 18 have been amended as shown above and new claims 21 through 34 have been added. As noted below, claims 16 and 18 have been amended to remove their dependency upon withdrawn claims 2 and 1, respectively, in order to obviate their rejection under 35 USC § 112, 2<sup>nd</sup> paragraph. The remaining amendments have been made for primarily grammatical reasons, and not for the sake of patentability.

The amendments to claims 1, 2, 3, 5, 6, 9, 11, 12, 14, 16 and 18 provided herein should be entered by the examiner because they are supported by the as-filed Specification and do not add any new matter to the Application. Further, the amendments neither raise new issues nor require further search, and they place the claims in condition for allowance.

New claims 21 through 34 should be entered because they are dependent upon the elected claims under examination and read upon the subject matter of the previously elected Claim Group II (*See Response to Restriction Requirement filed on May 20, 2005*). In addition, these new claims are supported by the as-filed Specification, do not add new matter to the Application, and do not require further search. Specific support for the new claims can be found in the Specification, as filed. In particular, support for new claims 21 through 26 can be found on pages 65 through 67; and support for new claims 27 and 31 can be found in Figure 1 and on pages 22, 23, 33, 37 and 38; and support for new claims 28 through 30 and 32 through 34 can be found in Section 5 of the Specification, on pages 37 and 38.

## THE REJECTIONS

### Claim Rejections under 35 USC § 112, 2<sup>nd</sup> paragraph

Claims 16 and 18 have been amended to remove their dependency upon withdrawn claims 2 and 1, respectively, thereby obviating the rejection under 35 USC § 112, 2<sup>nd</sup> paragraph. At the time the instant Application was filed, fees were paid to cover the cost of examination of a total of 20 claims, of which three could be independent. These amendments change the number of pending independent claims from two to four. Consequently, a fee transmittal form is being submitted herewith to cover the cost of the one additional independent claim, beyond the total of three covered by the basic filing fee. The fee transmittal form also covers the cost of filing the 14 new dependent claims, which are ultimately dependent upon either claim 16 or 18, or both.

### Claim Rejections under 35 USC § 102/103

Claims 16 through 18 and 20 stand rejected under 35 USC § 102(b) for allegedly being anticipated by Hirashima *et al.* (1986) *PNAS* 83:7726-7730 or, alternatively, under 35 USC § 103(a) for allegedly being obvious over Hirashima *et al.* In addition, claims 18 through 20 stand rejected under 35 USC § 102(a) for allegedly being anticipated by Sijen *et al.* (2001) *Cell* 107:465-476 or, alternatively, under 35 USC § 103(a) for allegedly being obvious over Sijen *et al.*

### Rejections under 35 USC § 102:

Applicants traverse the rejections under 35 USC § 102(b) and 35 USC § 102(a), and respectfully submit that the rejections are improper, for the following reasons.

**“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.”** *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). .... **“The identical invention must be shown in as complete detail as is contained in the ... claim.”** *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim....”

MPEP, 8<sup>th</sup> Ed., Rev. 2, May 2004, § 2131, p. 2100-73 (emphasis added).

With respect to Hirashima *et al.* (1986) *PNAS* 83:7726-7730, hereinafter called “Hirashima,” Applicants respectfully point out that, in contrast to the claimed invention, Hirashima teaches the use of an anti-sense “mRNA-interfering complementary RNA” (micRNA) that inhibits bacteriophage infection in *Escherichia coli* by binding to the Shine-Dalgarno sequence of viral transcripts, thereby presumably blocking ribosome binding and translation initiation. Hirashima does **NOT** disclose the use of a “universal interfering RNA,” that **induces RNA interference (RNAi) and promotes the degradation** of chimeric RNA transcripts bearing a “universal target RNA.” In fact, the experiments described in Hirashima were conducted in a prokaryotic host (i.e., *E. coli*) that, like all prokaryotes, is incapable of RNA interference. In view of these critical differences between the teachings of Hirashima and the claimed invention, the rejection under 35 USC § 102(b) is unsupported by the art and should be withdrawn.

With respect to Sijen *et al.* (2001) *Cell* 107:465-476, hereinafter called “Sijen,” Applicants respectfully point out that, although Sijen teaches the induction of RNA interference and resulting degradation of chimeric RNA transcripts, in contrast to the claimed invention, Sijen does not disclose the use of a single “universal interfering RNA,” to induce RNA interference and promote the degradation of a **plurality of chimeric transcripts bearing different “subject RNAs” and the same “universal target RNA.”** In view of these critical differences between the teachings of Sijen and the claimed invention, the rejection under 35 USC § 102(a) is also unsupported by the art and should be withdrawn.

#### **Rejections under 35 USC § 103:**

Applicants traverse the rejection under 35 USC § 103(a) in view of Hirashima and the rejection under 35 USC § 103(a) in view of Sijen, and respectfully submit that the rejections are (a) improper, and (b) fail to establish a *prima facie* case of obviousness.

#### ***Rejections are improper:***

As a first matter, Applicants note that MPEP § 706.02(j), in relevant part, instructs:

“After indicating that the rejection is under 35 U.S.C. 103, the examiner should set forth in the Office action: (A) the relevant teachings of the prior art relied upon, preferably with reference to the relevant column or page number(s) and line number(s) where appropriate, (B) the difference or differences in the claim over the applied reference(s), (C) the proposed modification of the applied reference(s) necessary to arrive at the claimed subject matter, and (D) an explanation why one of ordinary skill in the art at the time the invention was made would have been motivated to make the proposed modification.”

MPEP, 8<sup>th</sup> Ed., Rev. 2, May 2004, § 706.02(j), p. 700-46.

With all due respect, Applicants assert that, unfortunately, only the first of the four steps outlined above were undertaken during the preparation of the instant Office Action. Applicants further note that MPEP § 706.02(j), in relevant part, indicates: “It is important for an examiner to properly communicate the basis for a [35 USC § 103] rejection so that the issues can be identified early and the applicant can be given fair opportunity to reply.” MPEP, 8<sup>th</sup> Ed., Rev. 2, May 2004, § 706.02(j), p. 700-46. For the record, Applicants now find themselves in the difficult position of attempting to respond to a 35 USC § 103 rejection without a clear understanding of the basis upon which that rejection has been made, and, more specifically, without the examiner having identified “the proposed modification of the applied reference(s) necessary to arrive at the claimed subject matter.”

As a second matter, Applicants note that MPEP § 706.02(j), in relevant part, also instructs:

“The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. “To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.” *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).”

MPEP, 8<sup>th</sup> Ed., Rev. 2, May 2004, § 706.02(j), p. 700-46.

Applicants respectfully assert that the examiner has failed to follow the teachings provided in *Ex parte Clapp*, and MPEP § 706.02(j). Consequently, the rejections are improper and should be withdrawn.

***Rejections fail to establish a proper prima facie case of obviousness:***

As stated in MPEP § 2143:

“To establish a prima facie case of obviousness, three basic criteria must be met. First, **there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference** or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, **the prior art reference (or references when combined) must teach or suggest all the claim limitations.**”

MPEP, 8<sup>th</sup> Ed., Rev. 2, May 2004, § 2143, p. 2100-129 (emphasis added).

With respect to the teachings of both Hirashima and Sijen, Applicants respectfully assert that (a) as shown above, the applied references do not teach or suggest all of the limitations of claims 16 through 20, and (b) absent impermissible hindsight, there is no suggestion or motivation to modify the teachings to produce the claimed invention either within the references, or within the knowledge generally available to one of ordinary skill in the art. Since (a) the prior art references do not teach or suggest all of the claim limitations, (b) the examiner has failed to identify how the references are to be modified to arrive at the claimed invention, and (c) the examiner has failed to explain where the suggestion or motivation to modify the references can be found, the examiner has failed to make a proper showing to establish a *prima facie* case of obviousness. Consequently, the rejections under 35 USC § 103(a) should be withdrawn.

**CONCLUSIONS**

Claims 16 through 34 are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. Should the examiner determine that additional issues remain that might be resolved by a telephone conference, he is invited to contact the undersigned. Should any of claims 16 through 34 be found to be in condition for allowance, Applicants respectfully request the rejoinder of process (i.e., method) claims 1 through 15, in accordance with the provisions described in MPEP § 821.04.

It is believed that neither an extension of time, nor payment of any additional fee – **beyond that provided in the accompanying fee transmittal letter** – is required in connection with this communication. However, if an extension of time and a corresponding extension fee, or any other fee, is required, such an extension of time is hereby petitioned for and the Commissioner is authorized to charge any fees, or credit any overpayment, to Deposit Account No. **50-1627**.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'H. Ley III', with a long horizontal flourish extending to the left.

Herbert L. Ley III, Ph.D.  
Registration No. 53,215

Intellectual Property Department  
**Myriad Genetics, Inc.**  
(Customer No. 26698)  
320 Wakara Way  
Salt Lake City, UT 84108  
Telephone: 801-584-3600  
Fax: 801-883-3871

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